REMARKS

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

Claims 89-112 and 148 are pending. Claim 89 is amended. Support for these amendments is found in Figures 20C, 21F, and 23F as well as page 40, lines 14-34; page 41, lines 1-14; page 41, line 28 to page 42, line 5; page 45, line 21 to page 46, line 2; page 46, line 29 to page 47, lines 29-39; and page 49, lines 15-20.

The rejection of claims 89, 93, and 148 under 35 U.S.C. § 102(b) as anticipated by Lipshutz et al., *Biotechniques* 19(3):442-447 (1995) ("Lipshutz") is respectfully traversed.

Lipshutz relates to a method of light-directed chemical synthesis to create high-density arrays of oligonucleotide probes, which can be used for detection of hybridized targets. In particular, this reference discloses the synthesis of an array of oligonucleotides in which linker molecules with a photochemically removable protective group are attached to a solid substrate. Light is directed through a photolithographic mask to specific areas of the surface, activating those areas for chemical coupling. The first of a series of nucleosides is incubated with the array, and chemical coupling occurs at those sites that have been illuminated in the preceding step. Next, light is directed to a different region of the substrate through a new mask, and the chemical cycle is repeated. The process is repeated.

In contrast, claim 89 (and its dependent claims 90-112 and 148) is directed to "[a] method of forming arrays of oligonucleotides on a solid support comprising: providing a solid support having an array of positions each suitable for attachment of an oligonucleotide; attaching linkers to the solid support surfaces, wherein the linkers are suitable for coupling oligonucleotides to the solid support, at each of the array positions; and forming an array of a plurality of capture oligonucleotides on the solid support by a series of cycles, each of the cycles comprising activating selected array positions for attachment of multimer nucleotides and attaching multimer nucleotides at the activated array positions. The multimer nucleotides are selected so that the capture oligonucleotides formed by attachment of a plurality of the multimer nucleotides at each activated array position have nucleotide sequences selected to hybridize with complementary oligonucleotide target sequences under uniform hybridization conditions across the array of oligonucleotides."

Lipshutz neither discloses nor suggests forming an array of a plurality of capture oligonucleotides on the solid support by a series of cycles, each of the cycles

comprising activating selected array positions for attachment of multimer nucleotides and attaching multimer nucleotides at the activated array positions. Instead, Lipshutz teaches attaching single nucleosides to sites that have been illuminated in the preceding step. As amended the claims can no longer be properly construed to read on Lipshutz's synthesis of oligomers. Simply stated, repeatedly adding one nucleoside to an array at a time is not the same as repeatedly putting a multimer on the array.

A further distinction is that Lipshutz neither discloses nor suggests using multimer nucleotides which are selected so that the capture oligonucleotides formed by attachment of a plurality of the multimer nucleotides at each activated array position hybridize to complementary oligonucleotides under uniform hybridization conditions across the array of oligonucleotides, as required by the claims of the present application. In contrast, Lipshutz identifies the generation of signal from GC-rich and AT-rich probes (which have different hybridization strengths) in the same experiment as an "important challenge" to be met for broad implementation of the disclosed method (see page 7 of 7, col. 1, lines 21-30). This is an important distinction between Lipshutz and the claimed invention. In particular, the probes in Lipshutz's array carry the burden of both detecting a target nucleic acid and generating a signal correlated to detection of the target. Designing a plurality of capture probes capable of detecting and signaling detection of a plurality of different nucleic acid targets at one time on a single array (i.e. under uniform hybridization conditions) is a difficult task using Lipshutz's technology. Moreover, since Lipshutz's capture probes must be capable of accomplishing the diverse tasks of detection and signaling, its system is particularly susceptible to producing false signals. By contrast, detection and signaling of such detection can be readily and accurately achieved with the device produced by the method of the present invention, because the above characteristics of the capture probes.

One example of how the device produced in accordance with the present invention achieves such improved results involves its use with ligase detection reaction ("LDR"). As shown, for example, in Figure 3 of the present application, the presence or absence of a particular base in a target nucleic acid sequence is detected by LDR using probes having target specific portions (shown as hatched). One of those probes has a capture probe specific portion Z1, Z2, Z3, or Z4 (shown as solid) which does not bind to the target nucleic acid but is important in the subsequent step of array capture. When target nucleic acid is present, the probes are ligated and the sample is contacted with an array so that capture probe-specific portion Z1, Z2, Z3, or Z4 hybridizes to its complementary capture probes.

When the target nucleic acid is in the sample during LDR (so that the LDR probes ligate), that ligation event will form a product having a marker which can be detected when that product is hybridized to a capture probe on the array at capture probe-specific portion Z1, Z2, Z3, or Z4. Use of a device produced in accordance with the present invention in an LDR process is only one example of how that device can be utilized. The important thing to remember is that, with that device, detection and signaling can be carried out separately, facilitating the array capture and detection of a plurality of different nucleic acids at one time.

The outstanding office action continues to impermissibly maintain the position that the "under uniform hybridization conditions" limitation is a statement of intended use which does not distinguish the claimed method. This appears to be based on a failure to appreciate that the above-described benefits of the claimed invention are correlated to the steps of the claimed method. In particular, the claimed method calls for forming an array of capture oligonucleotides on a solid support by carrying out cycles of activating selected array positions and attaching multimers to the activated array positions. That forming step is carried out to produce an array of capture oligonucleotides having nucleotide sequences selected to hybridize to complementary oligonucleotide target sequences under uniform hybridization conditions across the array of oligonucleotides. The "uniform hybridization conditions across the array" limitation characterizes the nucleotide content of the capture oligonucleotides formed on the support as a result of cyclically attaching multimers having a nucleotide content which collectively dictate that of the capture oligonucleotides. Therefore, this limitation does indeed limit the claimed method.

As explained on page 35, lines 11-12 of the present application, the melting temperature of DNA/DNA duplexes (i.e. the temperature at which 2 DNA molecules hybridize to one another can be estimated as $[4n(G{\cdot}C) + 2m(A{\cdot}T)]$ °C. Thus, the number of Gs, Cs, As, and Ts in a DNA molecule affects the temperature at which that DNA molecule hybridizes to its complementary target molecule. By requiring that the claimed capture oligonucleotides formed on the array to hybridize with complementary oligonucleotide target sequences under uniform hybridization conditions across the array, it is apparent that the capture oligonucleotides are designed with a nucleotide content that permits the capture oligonucleotides to bind their complementary target molecule under under uniform hybridization conditions. As such, the uniform hybridization conditions limitation of the claims constitutes a limitation which must be given weight in determining whether the claimed method is distinguishable from the invention of Lipshutz. This conclusion is not

altered by the absence of any specific sequence in the claims. The selection of a plurality of capture oligonucleotide probes across the array which hybridize under uniform conditions requires that those probes have sequences with similar melting temperatures. Nothing more is needed to distinguish the claimed method from that of Lipshutz.

The outstanding office action is incorrect in stating that the target sequences can be any sequence. As is clear from the language of the claims, the target sequences are those complementary to claimed capture oligonucleotides. By requiring such complementarity and that the claimed plurality of capture oligonucleotides formed on the array hybridize with complementary oligonucleotide target sequences under uniform hybridization conditions across the oligonucleotide array, it is apparent that claims are not simply calling for any target sequence or any capture oligonucleotide. The claims are instead calling for a method of forming an array where the capture oligonucleotides formed on the array all hybridize with complementary oligonucleotide target sequences under uniform hybridization conditions. There is no teaching of this anywhere in Lipshutz. The U.S. Patent and Trademark Office's reliance on the statement in Lipshutz regarding a fixed set of hybridizing conditions says nothing about whether all the capture oligonucleotides formed on the array hybridize with complementary oligonucleotide target sequences under uniform hybridization conditions. Indeed, the page 443 of Lipshutz teaches away from this concept by stating that under a fixed set of hybridization conditions the fractions of probes bound to targets will vary. As noted above, the ability of the plurality of capture oligonucleotides formed on an array to hybridize with complementary oligonucleotide target sequences under uniform hybridization conditions constitutes a significant advantage over arrays lacking this feature, because the formed arrays can permit detection of a target separately from signaling such detection.

Accordingly, the rejection based on Lipshutz is improper and should be withdrawn.

The rejection of claims 89 and 93 under 35 U..C. § 102(b) as anticipated by Fodor et al., *Nature* 364:555-556 (1993) ("Fodor II") is respectfully traversed.

Fodor II relates to the synthesis of biological arrays by attaching linkers modified with photochemically removable protecting groups to a solid substrate. Light is directed through a photolithographic mask to specific areas of the surface effecting localized photodeprotection. The first of a series of chemical building blocks (e.g., hydroxyl photoprotected deoxynucleosides) is incubated with the surface, and chemical coupling

occurs at those sites which have been illuminated in the preceding step. Next, light is directed to a different region of the substrate through a new mask, and the chemical cycle is repeated.

Fodor II neither discloses nor suggests forming arrays of oligonucleotides on a solid support comprising: providing a solid support having an array of positions each suitable for attachment of an oligonucleotide; attaching linkers to the solid support surfaces, wherein the linkers are suitable for coupling oligonucleotides to the solid support, at each of the array positions; and forming an array of a plurality of capture oligonucleotides on the solid support by a series of cycles, each of the cycles comprising activating selected array positions for attachment of multimer nucleotides and attaching multimer nucleotides at the activated array positions. The multimer nucleotides are selected so that the plurality of capture oligonucleotides formed by attachment of a plurality of the multimer nucleotides at each activated array position hybridize with complementary oligonucleotide target sequences under uniform hybridization conditions across the array of oligonucleotides, as required by the claims of the present application. Accordingly, for substantially the reasons noted above, the rejection based on Fodor II is improper and should be withdrawn.

The rejection of claims 89-93, 96-97, 109, 111, and 148 under 35 U.S.C. § 102(e) as anticipated by U.S. Patent No. 5,700,637 to Southern et. al., is respectfully traversed.

Southern discloses an apparatus and a method for analyzing polynucleotide sequences as well as a method of generating oligonucleotide arrays. The oligonucleotides forming the array are only disclosed to be formed from conventional nucleotides. Thus, Southern suffers from the same deficiencies as Lipshutz and fails to teach forming arrays of oligonucleotides on a solid support comprising: providing a solid support having an array of positions each suitable for attachment of an oligonucleotide; attaching linkers to the solid support surfaces, wherein the linkers are suitable for coupling oligonucleotides to the solid support, at each of the array positions; and forming an array of a plurality of capture oligonucleotides on the solid support by a series of cycles, each of the cycles comprising activating selected array positions for attachment of multimer nucleotides and attaching multimer nucleotides at the activated array positions. The multimer nucleotides are selected so that the plurality of capture oligonucleotides formed by attachment of a plurality of the multimer nucleotides at each activated array position have nucleotide sequences selected to hybridize with complementary oligonucleotide target sequences under uniform hybridization

conditions across the array of oligonucleotides, as claimed. Accordingly, the rejection based on Southern should be withdrawn.

The rejection of claims 89, 91, 93, 96, 111, and 148 under 35 U.S.C. § 102(e) as anticipated by U.S. Patent No. 5,837,832 to Chee et. al., is respectfully traversed.

Chee teaches arrays of nucleic acid probes on biological chips. Chee fails to teach forming arrays of oligonucleotides on a solid support comprising: providing a solid support having an array of positions each suitable for attachment of an oligonucleotide; attaching linkers to the solid support surfaces, wherein the linkers are suitable for coupling oligonucleotides to the solid support, at each of the array positions; and forming an array of a plurality of capture oligonucleotides on the solid support by a series of cycles, each of the cycles comprising activating selected array positions for attachment of multimer nucleotides and attaching multimer nucleotides at the activated array positions. The multimer nucleotides are selected so that the plurality of capture oligonucleotides formed by attachment of a plurality of the multimer nucleotides at each activated array position have nucleotide sequences selected to hybridize with complementary oligonucleotide target sequences under uniform hybridization conditions across the array of oligonucleotides, as claimed. Therefore, Chee is distinguishable from the claimed invention for substantially the same reasons noted above, and the rejection based on this rejection should be withdrawn.

The rejection of claims 89-97, 109, 111-112, and 148 under 35 U.S.C. § 102(e) as anticipated by U.S. Patent No. 5,510,270 to Fodor et al. ("Fodor I") is respectfully traversed.

Fodor I relates to a method for synthesizing and screening polymers on a solid substrate. The method includes providing a substrate which may include linker molecules on its surface. On the substrate or a distal end of the linker molecules, a functional group with a protective group is provided. The protective group may be removed upon exposure to radiation, electric fields, electric currents, or other activators to expose the functional group. Using photolithographic methods, the protective group is removed in first selected regions and the substrate is contacted with a first monomer which reacts with the functional group. Thereafter, second selected regions are deprotected and exposed to a second monomer which reacts with the exposed functional group. These steps are repeated until the substrate includes desired polymers of desired lengths. Monomers may include amino acids, nucleotides, pentoses, and hexoses.

Fodor I neither discloses nor suggests forming arrays of oligonucleotides on a solid support comprising: providing a solid support having an array of positions each suitable for attachment of an oligonucleotide; attaching linkers to the solid support surfaces, wherein the linkers are suitable for coupling oligonucleotides to the solid support, at each of the array positions; and forming an array of a plurality of capture oligonucleotides on the solid support by a series of cycles, each of the cycles comprising activating selected array positions for attachment of multimer nucleotides and attaching multimer nucleotides at the activated array positions. The multimer nucleotides are selected so that the plurality of capture oligonucleotides formed by attachment of a plurality of the multimer nucleotides at each activated array position have nucleotide sequences selected to hybridize with complementary oligonucleotide target sequences under uniform hybridization conditions across the array of oligonucleotides, as required by the claims of the present application. Therefore, Fodor I is distinguishable from the claimed invention for substantially the same reasons noted above, and the rejection based on this reference should be withdrawn.

The rejection of claims 89-94, 96-97, 109, 111-112, and 148 under 35 U.S.C. § 102(e) as anticipated by U.S. Patent No. 5,527,681 to Holmes ("Holmes") is respectfully traversed.

Holmes relates to methods, devices, and compositions for synthesis and use of diverse molecular sequences on a substrate. In particular, this reference discloses the synthesis of an array of polymers in which individual monomers in a lead polymer are systematically substituted with monomers from one or more basic sets of monomers. On the substrate or a distal end of linker molecules, a functional group with a protective group is provided. The protective group may be removed upon exposure to a chemical reagent, radiation, electric fields, electric currents, or other activators to expose the functional group. Using photolithographic methods, the protective group is removed in first selected regions and the substrate is contacted with a first monomer which reacts with the functional group. Thereafter, second selected regions are deprotected and exposed to a second monomer which reacts with the exposed functional group. These steps are repeated until the substrate includes desired polymers of desired lengths. Monomers may include amino acids, nucleotides, pentoses, and hexoses. Holmes neither discloses nor suggests forming arrays of oligonucleotides on a solid support comprising: providing a solid support having an array of positions each suitable for attachment of an oligonucleotide; attaching linkers to the solid support surfaces, wherein the linkers are suitable for coupling oligonucleotides to the solid

support, at each of the array positions; and forming an array of a plurality of capture oligonucleotides on the solid support by a series of cycles, each of the cycles comprising activating selected array positions for attachment of multimer nucleotides and attaching multimer nucleotides at the activated array positions. The multimer nucleotides are selected so that the plurality of capture oligonucleotides formed by attachment of a plurality of the multimer nucleotides at each activated array position have nucleotide sequences selected to hybridize with complementary oligonucleotide target sequences under uniform hybridization conditions across the array of oligonucleotides, as required by the claims of the present application. Therefore, Holmes is distinguishable from the claimed invention for substantially the same reasons noted above, and the rejection based on this reference should be withdrawn.

The rejection of claims 89-97, 109, 111, 112, and 148 under 35 U.S.C. § 112 (2^{nd} para.) for indefiniteness is respectfully traversed in view of the above amendments.

In view of the all of the foregoing, applicants submit that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

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